Niemann-Pick disease type C: analysis of 7 patients

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Background: **Niemann-Pick disease type C (NP-C), derived from mutation of the *NPC1* or *NPC2* gene, is one of the recessive lysosomal lipid storage disorders that are difficult to diagnose and treat. Since NP-C has been rarely reported in China, we reviewed 7 patients with NP-C.**

Methods: **The 7 patients had been diagnosed with NP-C from 2007 to 2010 at our department and their laboratory and clinical data were analyzed.**

Results: **The 7 patients, 5 males and 2 females, included 4 patients of late infantile subtype and 3 patients of juvenile subtype, in which patients 2 and 3 were siblings. Their clinical symptoms occurred from 4 to 10 years of age, exhibiting as progressive cognitive and language impairment as well as motor retrogression. Six patients were caught by focal or generalized seizures from 1 to 4 years after the onset of the disease. Vertical supranuclear gaze palsy, dysarthria, dysphagia, internal rotation and adduction of bilateral hands and splenomegaly occurred following the progress of clinical symptoms. Five patients had laughter-cataplexy. MRI showed mild brain atrophy in 6 patients. Reduction of total cholesterol, high density lipoprotein cholesterol and low density lipoprotein cholesterol occurred in 6 patients. Sea-blue cells and Niemann-Pick cells were found in bone marrow smears. The activity of acid sphingomyelin enzyme was normal or only slightly lower. Supporting or symptomatic treatment improved common clinical symptoms.**

Conclusions: **NP-C is a rare autosomal recessive inherited lysosomal storage disease that affects the intellectual development of children and may lead to dementia, vegetative state or death. Clinical features of this disease include vertical supranuclear gaze palsy, seizures and cataplexy. Laboratory features include abnormal plasma cholesterol level, and sea-blue cells and Niemann-Pick cells in bone marrow smears. The treatments of the disease include supporting or symptomatic administration.**

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Original article

Introduction

Niemann-Pick disease type C (NP-C), first described by Niemann (1914), and characterized pathologically by Pick (1933), is a rare autosomal recessive lysosomal lipid storage disorder with an estimated incidence of 1/120 000 live births. It stems from inherited deficiencies of lysosomal proteins involved in intracellular lipid-trafficking proteins and is characterized by accumulation of unesterified cholesterol and glycolipids in the endosomal/lysosomal system due to mutations of either the *NPC1* (95% of families) or *NPC2* genes. The functional defects of *NPC1* and *NPC2* gene products lead to characteristic intracellular transport abnormalities of cellular cholesterol, fat and nerve sheath glycosides sphingosine and cause these lipids within the body in the secondary/soluble enzyme accumulate.[1-3] The clinical features of NP-C include vertical supranuclear gaze palsy, cerebellar ataxia, dysarthria, dysphagia, progressive dementia, cataplexy, seizures and dystonia,[4-6] which affect the patient's development and life quality severely. The average age of deaths due to NPC1 disease is 16.2 years, and one-half of them died before the age of 12.5 years.[4]

Limited progress has been made in treatment of NP-C in North America or Europe. The strategies of the treatment include weekly cyclodextrin administration to normalize cholesterol metabolism,[6] and inhibition of lysosomal acid lipase by thiadiazole carbamates[7] and miglustat (Zavesca) to stabilize neurological pathology.[8] However, there are few reports on NP-C in Chinese children except two reports from Taiwan province.[9,10] In order to improve the early diagnosis

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and treatment of NP-C, we reviewed 7 patients with NP-C treated at our Department of Pediatric Neurology.

Methods

Patients

The 7 patients who had been treated at our department from 2007 to 2010 comprised 5 males and 2 females with the onset of the disease at age of 4 to 10 years. Their clinical characteristics are shown in Table 1. Patients 2 and 3 were siblings. According to the method described by Wraith,[11] the patients were grouped into one of the five subtypes by age: neonatal subtype (≤3 months), early infantile subtype (3 months-2 years), late infantile subtype (2-6 years), juvenile subtype (6-15 years), and adolescent and adult subtype (≥15 years).

Diagnostic criteria

The patients were enrolled with the reported diagnostic criteria:[12] (1) slow progress of central nervous system degradation characterized by progressive ataxia, dysarthria, dysphagia, language disorder, dystonia and seizure; (2) progressive vertical supranuclear gaze palsy; (3) hepatosplenomegaly, predominantly in the spleen; (4) sea-blue histiocyte in bone marrow morphology smears; and (5) normal or slightly abnormal activity of acid sphingomyelin enzyme.

Laboratory examination

Laboratory examination included urine metabolite screening, blood biochemical index, genetic diseases-related indexes (lactic acid, blood ammonia, uretic amino acid and organic acid) and activity of acid sphingomyelin enzyme. Revised Wechsler Intelligence Scale for Children (C-WISC) was used to test the intelligence of the patients. Abdominal B-ultrasonography was performed to check the abdominal organs. MRI of the brain was performed with a 1.5T machine. Video-electroencephalography (EEG) was conducted using scalp and ear lobe electrodes positioned according to the 10-20 International System. Bone marrow aspiration was made under local anesthesia and the smears were stained with the Wright-Giemsa method.

Treatment and follow-up

All patients were given supporting and symptomatic treatment including antiepileptic treatment for those with seizures and surgery for those with difficulty in swallowing.

The diagnosis, treatment and study of the patients were approved by the Ethic Committee of the hospital and written informed consents were obtained from all patients.

Results

Laboratory examination

The results of urine metabolic screening were normal in all patients. The activity of acid sphingomyelin enzyme was normal or slightly lower. Biochemical examination revealed that the levels of total cholesterol, high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were reduced

Table 1. Clinical characteristics of the 7 patients with Niemann-Pick disease type C

#	Gender	Onset age	Current age	Onset symptom	Age at seizure	Seizure types	Bone marrow smears	Electroencephalography	TCHO (3.4-5.2)	HDL-C (1-1.5)	LDL-C (2.1-3.1)	Activity of acid phosphatase (nmol/17h/mgPr)	Antiepileptic drugs
1	F	6y, L	12y10m	Intellectual and motor retrogression	7 y	Partial secondary generalized	Sea blue cells	Anterior head spike-slow wave, slow wave	3.06	0.86	2.24	5.7 (7-13.7)	TPM + VPA
2	M	4y, L	14y8 m	Intellectual retrogression	9 y	Partial	Sea blue cells	Anterior head slow wave, spike-slow wave	2.49	1.16	1.04	4.5 (7-13.7)	TPM + CZP + VPA
3	M	4y, L	7y9 m	Cognitive impairment	7.5 y	Partial	Sea blue cells, N-P cells	Anterior head spike wave, spike-slow wave, bilaterally asynchronous	2.9	1.0	1.68	Normal	TPM
4	M	10y, J	14y11m	Motor impairment	ND	ND	Sea blue cells	ND	2.46	0.56	1.63	Normal	ND
5	M	10y, J	16y6 m	Language impairment	14 y	Partial secondary generalized	Sea blue cells, N-P cells	Bi- or unilateral anterior head spike-slow wave, slow wave, predominantly on right side	2.00	0.78	1.03	14 (17-40)	TPM
6	M	8y, J	13y10m	Motor impairment	12 y	Tonic-clonic	Sea blue cells	Bilaterally anterior head spike wave, spike-slow wave	2.95	1.09	1.57	Normal	TPM
7	F	5.5y, L	9y	Motor impairment	8 y	Partial secondary generalized	Sea blue cells, suspicious N-P cell	Bilateral frontal slow wave, multifocal spike wave, slow wave and spike-slow wave	3.77	0.85	2.32	Normal	VPA + LTG + LEV

F: female; M: male; TCHO: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; L: late infantile; J: juvenile; TPM: topiramate; VPA: valproic acid; CZP: clonazepam; LTG: lamotrigine; LEV: levetiracetam; ND: no data.

considerably in 6 patients.

Bone marrow smears showed that sea-blue cells were present in the bone marrow aspirations from the patients. The sea-blue cells were characterized by cytoplasm filled with dark blue granules varying in size but without obvious foaming (Fig. 1A). In bone marrow smears Niemann-Pick cells were noted in 2 patients but dubiously in one patient (Table 2). Niemann-Pick cells were characterized by a large cell body and a round- or oval-shaped and lateralized nucleus as single and abundant cytoplasm filled with hemophagocytes and round transparent drop-shaped vesicles that were mulberry-like or foam-like (Fig. 1B).

C-WISC showed a reduction in language ability and full scale IQs. Abdominal B-ultrasonograpy showed splenomegaly in all patients and hepatomegaly in 6 patients. Video-EEG showed abnormalities including slow waves, spike waves and spike-slow waves releasing from the anterior head. Cranial MRI demonstrated mild brain atrophy of the cerebellum and cerebrum in 6 patients (Fig. 2A and 2B; Tables 1 and 2).

Clinical features

The clinical features of the patients are shown in Tables 1 and 2. The symptoms of these patients were

Table 2. Clinical features of the 7 patients with Niemann-Pick disease type C

Features	Case number (%)
Language impairment (speed to slow down, slurred speech, dysarthria)	7 (100.0)
Cognition impairment, psychological changes	7 (100.0)
Dysphagia	7 (100.0)
Vertical supranuclear gaze palsy	7 (100.0)
Splenomegaly	7 (100.0)
Bilateral arm intort, wrist flexion	6 (85.7)
Cholesterol reduction	6 (85.7)
Hepatomegaly	6 (85.7)
Brain atrophy	6 (85.7)
Ataxia	5 (71.4)
Cataplexy	5 (71.4)
Pyramid sign	4 (57.1)
Icterus	2 (28.6)
Chorea	2 (28.6)

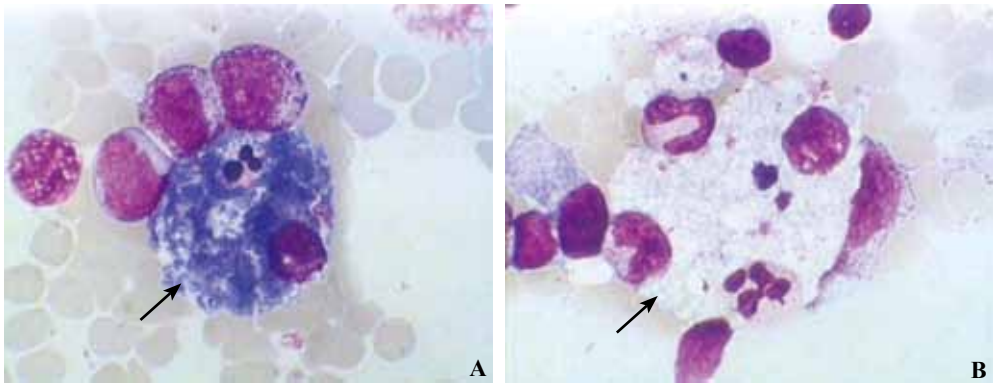

Fig. 1. Bone marrow smears from NP-C patients and Niemann-Pick cells shown by Wright-Giemsa's staining (original magnification × 100). **A:** sea-blue cells (arrow) characterized by a variety of dark blue granules without obvious foams in the cytoplasm; **B:** Niemann-Pick cells (arrow) characterized by big cell body, lateralized nucleus and a variety of cytoplasm filled with round-dropping transparent mulberry-like or foam-like bubbles.

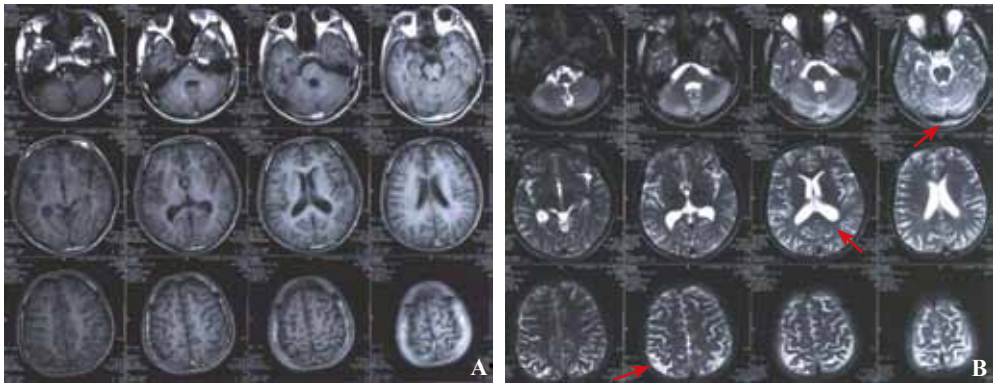

Fig. 2. Brain MRI of patient 5 showing mild atrophy in the bilateral cerebellum and cerebrum. **A:** T1-weighted image; **B:** T2-weighted image. Shrank gyrus and expanded ventricle volume shown by red arrows.

demonstrated as progressive cognitive and language impairments as well as motor retrogression. Seizures occurred within 1-4 years, including partial or generalized seizure (5 patients) and tonic-clonic seizure (1 patient). Vertical supranuclear gaze palsy occurred in all patients, accompanied with dysarthria or dysphagia in 7 patients and dystonia in 5. The dystonia occurred firstly to both-hands and feet and looked like intort, and then occurred to the whole body. Five patients had laughter-cataplexy. Moreover pyramidal sign was seen in 4 patients, and icterus or chorea in 2 patients.

Treatment and follow-up

All patients were subjected to supporting and symptomatic therapies. For patients with epilepsy, antiepileptic agents like topiramate, valproic acid, clonazepam, lamotrigine and levetiracetam were given in different combinations according to seizures and their situations. After the treatment, the frequency of seizure was reduced in the patients. Nasal feeding or gastrostomy was performed for patients with difficulty in drinking and swallowing, thus improving their general situation and nutritional status. With disease progression, 2 patients were paralyzed in bed with impairment of eye movement characterized by initially vertical saccadic difficulty, vertical saccadic fixture, horizontal saccadic difficulty, and finally limitation in the axis (Fig. 3).

An illustrative case

The male patient (No. 5 in Table 1) was admitted to the hospital for a seizure attack at age of 14 years. He had no obvious abnormality at birth and family history with normal intelligence and development. At 10 years old, he showed incoherent speech with little vague articulation and decreased academic performance. At 12 years old, he demonstrated ataxia, abnormal posture, and bilateral claw-like fingers. His speech speed slowed down with slurred articulation. He showed laughter-cataplexy, slobber, dysphagia and drinking cough sometimes. At 14 years old, he was attacked by seizures, exhibiting twisted head to one side, eyes upward, saccadic and stiff limbs. The seizures usually lasted about 20 minutes. The patient showed decreased appetite and gastrointestinal dysfunction such as diarrhea. Physical examination on admission demonstrated: (1) normal physical development, deficit in calculation, slowed speech speed, slurred articulation, ataxia, pes supinatusm while walking, bilateral upper arm involucrate and claw-like fingers, deeper insteps, right contracture of Achilles tendon, and bilateral limited vertical saccadic; (2) touchable spleen below ribs, myodynamia 4/5, hypertonia, bilateral knee tendon hyperreflexia and ankle clonus positive, bilateral Hoffmann sign positive and Babinski sign positive; (3) total bilirubin (TBIL) 23 μmol/L, direct bilirubin (DBIL) 5.01 μmol/L, total cholesterol 2.00 mmol/L, HDL-C 0.78 mmol/L, and LDL-C 1.03 mmol/L; (4) bilateral transduction delay in the peripheral pathway by audio-visual evoked potential; (5) splenomegaly at 5.3 cm below the rib edge with spleen portal internal diameter (ID) 0.8 cm and hepatomegaly at 2.3 cm below the rib edge by B-ultrasound; (6) unilateral or bilateral spike-slow waves and slow wave release in front head by EEG, predominantly on the right side and during sleep; (7) slight atrophy of the cerebrum and cerebellum shown by brain MRI; (8) active proliferation of sea-blue cells occasionally accompanied by Niemann-Pick cells in bone marrow smears; (9) activity of acidic sphingomyelinase at 14 nmol/17h/mgPr (normal 17-40 nmol/17h/mgPr). The patient was subjected to antiepileptic treatment with topiramate and followed up for 2 and half years.

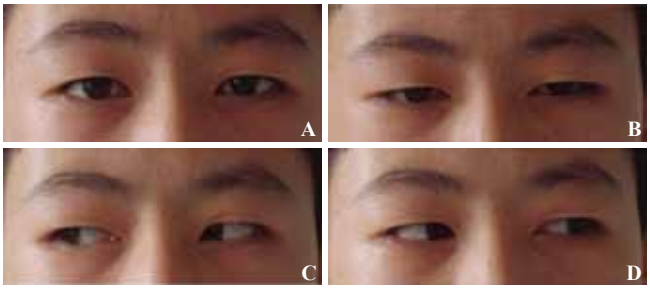

Fig. 3. Eye movements showing difficulty in vertical saccades whereas normal in horizontal saccades (patient 5). **A:** upward gaze; **B:** downward gaze; **C:** right gaze; **D:** left gaze.

Discussion

In the present study, the 7 patients with NP-C showed vertical supranuclear gaze palsy, seizures, abnormal EEG, intelligent and/or language impairment, sea-blue cells and splenomegaly. Brain atrophy, NP cells and abnormal LDL and HDL were observed in some patients. Supporting and symptomatic treatment improved some of these symptoms.

Unlike Niemann-Pick disease types A and B, which are associated with the deficiency of sphingomyelin degrading enzyme, NP-C is due to the mutation of the *NPC1* or *NPC2* gene.[2] The functional deficiency of *NPC1* and *NPC2* gene products in a NP-C patient leads to transportation abnormalities of cellular cholesterol and sphingosine and subsequent deposition of these substances in lysosomes of the liver, spleen and brain. As the deposition of cholesterol in lysosomes inhibits the activity of acid sphingomyelin to cause secondary

sphingomyelin deposition, this activity is normal or slightly reduced.[3,13] This finding is consistent with that of the present study or that reported previously.[14] In a drug-induced NP-C cellular model, sphingosine storage in the acid compartment results in calcium depletion in organelles, which leads to storage of cholesterol, sphingomyelin and glycosphingolipid in the compartment. Therefore, NPC1 causes altered calcium homeostasis, leading to the secondary storage of sphingolipids and cholesterol.[15] Other studies suggested that the up-regulation of ATP-binding cassette transporter objects A1 (ABCA1) in NP-C patients prevents cholesterol release from lysosomes and the reduction of HDL-C.[16,17] In the present study, most of the patients also showed abnormal cholesterol. Hence, plasma cholesterol can be determined as a useful biomarker.[16] Another laboratory characteristic in NP-C patients is sea-blue cells in bone marrow smears often, foamy cells sometimes and Niemann-Pick cells,[5,18] although it is not specific. In the current study, sea-blue cells were present in all patients and Niemann-Pick cells in 2 patients whereas suspicious Niemann-Pick cells were seen in 1 patient, suggesting that sea-blue cells are highly associated with NP-C.

In addition to laboratory examinations, image scanning, EEG and clinical signs are of diagnostic value for NP-C. Cranial MRI is able to show atrophy in the anterior part of the cerebellar vermis, thinning of the corpus callosum, cerebral atrophy with signal enhancement of the white matter due to secondary demyelination in some cases.[10,19-21] Some studies indicated that EEG examination could detect slow waves or alpha rhythm in NP-C patients.[21,22] Psychiatric changes are often followed by dystonia and cognitive impairment.[23] These findings are consistent with MRI and EEG findings in the present study. Clinical signs for NP-C include common features like cataplexy, seizures and dystonia. Neurological disorders consist mainly of cerebellar ataxia, dysarthria, dysphagia, and progressive dementia. The most characteristic sign is vertical supranuclear gaze palsy.[3,24-26] In the present study, all patients showed cognitive impairment, psychological changes, partial or generalized seizures and abnormalities in eye movement. Other symptoms of NP-C patients in our study included icterus, unexplained intermittent diarrhea and thrombocytolytic purpura. These signs may be induced by the infiltration and damage of sea-blue cells in the bone marrow, liver, spleen, lungs, gastrointestinal tract, lymph nodes or other organs.[11]

Because NP-C is one kind of genetic mutation disease and there is no specific therapy,[3,5,26] therapeutic attempts to date have focused on reduction of the accumulating molecules that are presumed to have direct or indirect toxic effects. Therefore, supporting and symptomatic managements of patients are crucial. Miglustat has been used in Europe and other countries for specific treatment of the neurological manifestations of NP-C,[3,8,27] but it is expensive and not available in China. Other strategies like bone marrow transplantation,[28,29] weekly cyclodextrin administration to normalize cholesterol metabolism,[6] and inhibition of lysosomal acid lipase by thiadiazole carbamates[7] are therapeutic potential for NP-C.

In summary, NP-C is a rare autosomal mutation disease that affects severely the life of patients and its diagnosis and treatment are complicated. It is a pity that our patients received neither genetical nor biochemical examination to confirm the disease. Further diagnosis is dependent on the determination of cholesterol esterification or filipin staining of cultured fibroblasts, or eventual test of the *NPC1* or *NPC2* gene.[11,16,30] The reported 7 NP-C cases are helpful to the diagnosis and treatment of the disease in the Chinese population.

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Ethical approval: This study was approved by the data inspectorate of China and by the regional committee for medical research ethics.
Competing interest: None.
Contributors: All authors reviewed relevant articles and they contributed to the intellectual content and approved the final version.

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